CLAIMS

1. An antibody composition comprising a recombinant antibody molecule which specifically binds to ganglioside GM2 and has complex type N-glycoside-linked sugar chains in the Fc region, wherein the complex type N-glycoside-linked sugar chains have a structure in which fucose is not bound to N-acetylglucosamine in the reducing end in the sugar chains.

2. The antibody composition according to claim 1, wherein the complex type N-glycoside-linked sugar chains are sugar chains in which 1-position of fucose is not bound to 6-position of N-acetylglucosamine in the reducing end through α-bond in the sugar chains.

3. The antibody composition according to claim 1 or 2, which specifically binds to a ganglioside GM2-expressing cell.

4. The antibody composition according to any one of claims 1 to 3, which has cytotoxic activity against a ganglioside GM2-expressing cell.

5. The antibody composition according to any one of claims 1 to 4, which has higher cytotoxic activity against a ganglioside GM2-expressing cell than a monoclonal antibody produced by a non-human animal-derived hybridoma.

6. The antibody composition according to claim 4 or 5, wherein the cytotoxic activity is antibody-dependent cell-mediated cytotoxic (ADCC) activity.

7. The antibody composition according to claim 4 or 5, wherein the cytotoxic activity is complement-dependent cytotoxic (CDC) activity.

8. The antibody composition according to any one of claims 1 to 7, which comprises complementarity determining region (CDR) 1, CDR 2 and CDR 3 of antibody molecule heavy chain (H chain) variable region (V region) consisting of the amino acid sequences represented by SEQ ID NOs:14, 15 and 16, respectively.

9. The antibody composition according to any one of claims 1 to 7, which comprises complementarity determining region (CDR) 1, CDR 2 and CDR 3 of antibody molecule light chain (L chain) variable region (V region) consisting of the amino acid sequences represented by SEQ ID NOs:17, 18 and 19, respectively.

10. The antibody composition according to any one of claims 1 to 9, which comprises complementarity determining region (CDR) 1, CDR 2 and CDR 3 of an antibody molecule heavy chain (H chain) variable region (V region) consisting of the amino acid sequences represented by SEQ ID NOs:14, 15 and 16, respectively; and CDR 1, CDR 2 and CDR 3 of antibody molecule light chain (L chain) V region consisting of the amino acid sequences represented by SEQ ID NOs:17, 18 and 19, respectively.

11. The antibody composition according to any one of claims 1 to 10, wherein the recombinant antibody is a human chimeric antibody or a human CDR-grafted antibody.

12. The antibody composition according to claim 11, wherein the human chimeric antibody comprises complementarity determining regions (CDRs) of heavy chain (H chain) variable region (V region) and light chain (L chain) V region of a monoclonal antibody which specifically binds to ganglioside GM2.

13. The antibody composition according to claim 12, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:20.

14. The antibody composition according to claim 12, wherein the light chain (L chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:21.

15. The human chimeric antibody composition according to any one of claims 12 to 14, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:20; and the light chain (L chain) V region of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:21.

16. The antibody composition according to claim 11, wherein the human CDR-grafted antibody comprises complementarity determining regions (CDRs) of heavy chain (H chain) variable region (V region) and light chain (L chain) V region of a monoclonal antibody which specifically binds to ganglioside GM2.

17. The antibody composition according to claim 16, which comprises complementarity determining regions (CDRs) of heavy chain (H chain) variable region (V

region) and light chain (L chain) V region of a monoclonal antibody which specifically binds to ganglioside GM2, and framework regions (FRs) of H chain V region and L chain V region of a human antibody.

18. The antibody composition according to claim 16 or 17, which comprises complementarity determining regions (CDRs) of heavy chain (H chain) variable region (V region) and light chain (L chain) V region of a monoclonal antibody which specifically binds to ganglioside GM2, framework regions (FRs) of H chain V region and L chain V region of a human antibody, and H chain constant region (C region) and L chain C region of a human antibody.

19. The antibody composition according to any one of claims 16 to 18, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:22 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Arg at position 38, Ala at position 40, Gln at position 43 and Gly at position 44 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:22.

20. The antibody composition according to any one of claims 16 to 18, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:23 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Arg at position 67, Ala at position 72, Ser at position 84 and Arg at position 98 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:23.

21. The antibody composition according to any one of claims 16 to 18, wherein the light chain (L chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:24 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Val at position 15, Tyr at position 35, Leu at position 46, Ser at position 59, Asp at position 69, Phe at position 70, Thr at position 71, Phe at position 72 and Ser at position 76 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:24.

22. The antibody composition according to any one of claims 16 to 18, wherein the light chain (L chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:25 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Met at position 4, Leu at

position 11, Val at position 15, Tyr at position 35, Ala at position 42, Leu at position 46, Asp at position 69, Phe at position 70, Thr at position 71, Leu at position 77 and Val at position 103 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:25.

23 The antibody composition according to any one of claims 16 to 19 or 21, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:22 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Arg at position 38, Ala at position 40, Gln at position 43 and Gly at position 44 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:22; and the light chain (L chain) V region of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:24 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Val at position 15, Tyr at position 35, Leu at position 46, Ser at position 59, Asp at position 69, Phe at position 70, Thr at position 71, Phe at position 72 and Ser at position 76 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:24.

24. The antibody composition according to any one of claims 16 to 18, 20 or 21, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:23 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Arg at position 67, Ala at position 72, Ser at position 84 and Arg at position 98 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:23; and the light chain (L chain) V region of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:24 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Val at position 15, Tyr at position 35, Leu at position 46, Ser at position 59, Asp at position 69, Phe at position 70, Thr at position 71, Phe at position 72 and Ser at position 76 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:24.

25. The antibody composition according to any one of claims 16 to 18, 20 or 22, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:23 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Arg at position 67, Ala at position 72, Ser at position 84 and Arg at position 98 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:23;

and the light chain (L chain) V region of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:25 or an amino acid sequence in which at least one amino acid residue selected from the group consisting of Met at position 4, Leu at position 11, Val at position 15, Tyr at position 35, Ala at position 42, Leu at position 46, Asp at position 69, Phe at position 70, Thr at position 71, Leu at position 77 and Val at position 103 is substituted with another amino acid residue in the amino acid sequence represented by SEQ ID NO:25.

26. The antibody composition according to any one of claims 16 to 20 or 23 to 25, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises an amino acid sequence selected from the group consisting of the amino acid sequences represented by SEQ ID NOs:22, 26, 27, 28, 29 and 30.

27. The antibody composition according to any one of claims 16 to 18 or 21 to 25, wherein the light (L chain) variable region (V region) of the antibody molecule comprises an amino acid sequence selected from the group consisting of the amino acid sequences represented by SEQ ID NOs:31, 32, 33, 34 and 35.

28. The antibody composition according to any one of claims 16 to 27, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises an amino acid sequence selected from the group consisting of the amino acid sequences represented by SEQ ID NOs:22, 26, 27, 28, 29 and 30; and the light chain (L chain) V region of the antibody molecule comprises an amino acid sequence selected from the group consisting of the amino acid sequences represented by SEQ ID NOs:31, 32, 33, 34 and 35.

29. The antibody composition according to any one of claims 16 to 19, 21, 23 or 26 to 28, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:26; and the light chain (L chain) V region of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:31 or 32.

30. The antibody composition according to any one of claims 16 to 19, 21 to 23 or 26 to 28, wherein the heavy chain (H chain) variable region (V region) of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:22; and the light chain (L chain) V region of the antibody molecule comprises the amino acid sequence represented by SEQ ID NO:32 or 35.

31. A transformant producing the antibody composition according to any one of claims 1 to 30, which is obtainable by introducing a DNA encoding an antibody molecule which specifically binds to ganglioside GM2 into a host cell.

32. The transformant according to claim 31, wherein the host cell is a cell in which genome is modified so as to have deleted activity of an enzyme relating to the synthesis of an intracellular sugar nucleotide, GDP-fucose, or an enzyme relating to the modification of a sugar chain in which 1-position of fucose is bound to 6-position of N-acetylglucosamine in the reducing end through α-bond in a complex type N-glycoside-linked sugar chain.

33. The transformant according to claim 31, wherein the host cell is a cell in which all of alleles on a genome encoding an enzyme relating to the synthesis of an intracellular sugar nucleotide, GDP-fucose, or an enzyme relating to the modification of a sugar chain in which 1-position of fucose is bound to 6-position of N-acetylglucosamine in the reducing end through α-bond in a complex type N-glycoside-linked sugar chain are knocked out.

34. The transformant according to claim 32 or 33, wherein the enzyme relating to the synthesis of an intracellular sugar nucleotide, GDP-fucose, is an enzyme selected from GDP-mannose 4,6-dehydratase (GMD) or GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase (Fx).

35. The transformant according to claim 34, wherein the GDP-mannose 4,6-dehydratase is a protein encoded by a DNA selected from the group consisting of the following (a) and (b):

(a) a DNA comprising the nucleotide sequence represented by SEQ ID NO:1;

(b) a DNA which hybridizes with the DNA consisting of the nucleotide sequence represented by SEQ ID NO:1 under stringent conditions and which encodes a protein having GDP-mannose 4,6-dehydratase activity.

36. The transformant according to claim 34, wherein the GDP-mannose 4,6-dehydratase is a protein selected from the group consisting of the following (a) to (c):

(a) a protein comprising the amino acid sequence represented by SEQ ID NO:2;

(b) a protein consisting of an amino acid sequence wherein one or more amino acid residue(s) is/are deleted, substituted, inserted and/or added in the amino acid sequence represented by SEQ ID NO:2 and having GDP-mannose 4,6-dehydratase activity;

(c) a protein consisting of an amino acid sequence which has 80% or more homology to the amino acid sequence represented by SEQ ID NO:2 and having GDP-mannose 4,6-dehydratase activity.

37. The transformant according to claim 34, wherein the GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase is a protein encoded by a DNA selected from the group consisting of the following (a) and (b):

(a) a DNA comprising the nucleotide sequence represented by SEQ ID NO:3;

(b) a DNA which hybridizes with the DNA consisting of the nucleotide sequence represented by SEQ ID NO:3 under stringent conditions and which encodes a protein having GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase activity.

38. The transformant according to claim 34, wherein the GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase is a protein selected from the group consisting of the following (a) to (c):

(a) a protein comprising the amino acid sequence represented by SEQ ID NO:4;

(b) a protein consisting of an amino acid sequence wherein one or more amino acid residue(s) is/are deleted, substituted, inserted and/or added in the amino acid sequence represented by SEQ ID NO:4 and having GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase activity;

(c) a protein consisting of an amino acid sequence which has 80% or more homology to the amino acid sequence represented by SEQ ID NO:4 and having GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase activity.

39. The transformant according to claim 32 or 33, wherein the enzyme relating to the modification of a sugar chain in which 1-position of fucose is bound to 6-position of N-acetylglucosamine in the reducing end through α-bond in a complex type N-glycoside-linked sugar chain is α1,6-fucosyltransferase.

40. The transformant according to claim 39, wherein the α1,6-fucosyltransferase is a protein encoded by a DNA selected from the group consisting of the following (a) to (d):

(a) a DNA comprising the nucleotide sequence represented by SEQ ID NO:5;

(b) a DNA comprising the nucleotide sequence represented by SEQ ID NO:6;

(c) a DNA which hybridizes with the DNA consisting of the nucleotide sequence represented by SEQ ID NO:5 under stringent conditions and which encodes a protein having α1,6-fucosyltransferase activity;

(d) a DNA which hybridizes with the DNA consisting of the nucleotide sequence represented by SEQ ID NO:6 under stringent conditions and which encodes a protein having α1,6-fucosyltransferase activity.

41. The transformant according to claim 39, wherein the α1,6-fucosyltransferase is a protein selected from the group consisting of the following (a) to (f):

(a) a protein comprising the amino acid sequence represented by SEQ ID NO:7;

(b) a protein comprising the amino acid sequence represented by SEQ ID NO:8;

(c) a protein consisting of an amino acid sequence wherein one or more amino acid residue(s) is/are deleted, substituted, inserted and/or added in the amino acid sequence represented by SEQ ID NO:7 and having α1,6-fucosyltransferase activity;

(d) a protein consisting of an amino acid sequence wherein one or more amino acid residue(s) is/are deleted, substituted, inserted and/or added in the amino acid sequence represented by SEQ ID NO:8 and having α1,6-fucosyltransferase activity;

(e) a protein consisting of an amino acid sequence which has 80% or more homology to the amino acid sequence represented by SEQ ID NO:7 and having α1,6-fucosyltransferase activity;

(f) a protein consisting of an amino acid sequence which has 80% or more homology to the amino acid sequence represented by SEQ ID NO:8 and having α1,6-fucosyltransferase activity.

42. The transformant according to claim 41, wherein the transformant is FERM BP-8470.

43. The transformant according to any one of claims 31 to 42, wherein the host cell is a cell selected from the group consisting of the following (a) to (i):

(a) a CHO cell derived from Chinese hamster ovary tissue;

(b) a rat myeloma cell line YB2/3HL.P2.G11.16Ag.20 cell;

(c) a mouse myeloma cell line NS0 cell;

(d) a mouse myeloma cell line SP2/0-Ag14 cell;

(e) a BHK cell derived from Syrian hamster kidney tissue;

(f) an antibody-producing hybridoma cell;

(g) a human leukemia cell line Namalwa cell;

(h) an embryonic stem cell;

(i) a fertilized egg cell.

44. A process for producing the antibody composition according to any one of claims 1 to 30, which comprises culturing the transformant according to any one of claims 31 to 43 in a medium to form and accumulate the antibody composition in the culture, and recovering and purifying the antibody composition from the culture.

45. The antibody composition according to any one of claims 1 to 32, which is obtainable by the process according to claim 44.

46. A pharmaceutical composition comprising the antibody composition according to any one of claims 1 to 30 and 45 as an active ingredient.

47. A therapeutic agent for diseases relating to a ganglioside GM2, comprising the antibody composition according to any one of claims 1 to 30 and 45 as an active ingredient.

48. The therapeutic agent according to claim 47, wherein the diseases relating to a ganglioside GM2 are cancer.